PULMONARY PHYSIOLOGY and CHRONIC PULMONARY DISEASES

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THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

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633 THIRD AVENUE
NEW YORK, N. Y. 10017

COMMITTEE:
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Dr. Reimann
Dr. Little

Application For Research Grant

Date: JANUARY 26, 1966

1. Name of Investigator: ROGER K. LARSON, M.D., F.A.C.P.

2. Title: Chief of Medicine

3. Institution & Address: FRESNO COUNTY HOSPITAL
FRESNO, CALIFORNIA

4. Project or Subject: TO TEST MORE THOROUGHLY THE HYPOTHESIS THAT THE SUSCEPTIBILITY TO DEVELOP OR NOT TO DEVELOP EMPHYSEMA IN SMOKERS IS GENETICALLY DETERMINED.

5. Detailed Plan of Procedure (Use additional pages if more space is required)

GENETIC INVESTIGATION OF EMPHYSEMA

I. Introduction

In a preliminary study supported by the Fresno County Tuberculosis and Health Association and reported at the American Federation for Clinical Research Meeting in January, 1965, the present investigator demonstrated an increased incidence of chronic obstructive pulmonary disease (C.O.P.D.) - like states in relatives of patients with C.O.P.D. as compared to the incidence in relatives of patients with other chest conditions not usually considered to be hereditary. (See attached summary tables and graphs.) This incidence was determined by detailed family history interviews of patients and the numbers were quite small. Only a few authors have reported on the familial occurrence of emphysema. In fact, McKusick, Goodman and Danks in an article entitled "Genetic Aspects of Respiratory Disease" published in 1963 commented on the lack of study of genetic factors in emphysema and gave the following explanation. "It is true that the conspicuous age-dependence of the disorder imposes difficulties. By the time the proband comes to attention, the parents are likely to be dead, the siblings are widely scattered and offspring are not yet old enough to show evidence of disease."

Two families studied in detail as part of this preliminary project showed such a high incidence of mild to severe chronic obstructive pulmonary disease as to suggest a genetic factor. (See attached tables and graphs.)

These studies are sufficiently encouraging to warrant a large full-scale objective study of the role of heredity in chronic obstructive pulmonary disease.

II. Research Plan

A. Specific Aims and Methods

It is the aim of this study to objectively assess the incidence of obstructive pulmonary phenomena in siblings and parents of patients seen at Fresno General Hospital with far advanced chronic obstructive pulmonary disease and compare this indicence to that found in a control population made up of the spouses of these relatives.

All patients admitted to the clinics or wards of F.G.H. with chronic obstructive pulmonary disease not known to be secondary to other diseases, such as far advanced pulmonary tuberculosis, pneumoconiosis, childhood allergic asthma, etc., will be included in the study. Diagnosis will be established by history, physical examination, x-ray and pulmonary function studies in each case. The names and addresses of all siblings and parents residing in the vicinity of Fresno will be obtained by interview. These relatives will then be contacted and asked to appear with their spouse at the hospital for investigation. This investigation will consist of the following:

1. Filling out a questionnair regarding symptoms, past history, occupational history and smoking history (see attached form), alcohol history.
2. Performance of at least three rapidly recorded timed inspired and expired vital capacities on a Collins 13.5 L spirometer with a recording speed of 16 mm/sec. From this the F.V.C., the F.E.V. 1% and MTF will be calculated for each patient. In addition, the ratio of mid-inspiratory to mid-expiratory flow rates will be obtained.
3. Determination of functional residual volume by the closed circuit helium technique.
4. ~~Determination of airway resistance by the body plethysmograph technique.~~
5. ~~Determination of sweat chlorides by pilocarpine iontophoresis and use of the Cotlove chloridimeter.~~
6. Chest x-ray.

All those having significantly abnormal findings on the above screening procedures will be asked to return for more detailed studies to include: 1) arterial PO_2, PCO_2 and pH; 2) carbon monoxide diffusing capacity; and 3) bilateral tomograms of the chest.

The incidence of abnormal findings in the siblings and parents will be compared with the incidence of abnormal findings in their spouses as a control group. Conventional tests of statistical significance will be applied to any difference found. The mean values for each test result will also be calculated for each group and the difference in means tested by the Student t test. An additional analysis will be made after dividing the groups into smoker and nonsmoker. categories to eliminate any bias that might be introduced by this potent environmental factor.

B. Significance of this Research

The etiology of emphysema remains obscure. A large amount of money is presently being invested in investigation of the cause but almost no attention has been directed to possible genetic aspects. The present investigator has done previous work supporting the role of environmental factors (principally cigarette smoke) in the pathogenesis of emphysema. That this is not the only factor, however, is indicated by two facts: 1) a small number of patients with emphysema have never smoked and 2) most people who smoke do not get emphysema. It is the purpose of this study to explore the hypothesis that a genetic factor determines the susceptibility of an individual to environmental factors (particularly cigarette smoke) in the development of emphysema. If this should be substantiated, it might help to identify the population at greatest risk and aid physicians in counseling their patients in the prophylaxis of this increasingly common and devastating disease.

6. Budget Plan:

a.	Salaries	14,840.00
b.	Expendable Supplies	1,000.00
c.	Other Expenses	
d.	Permanent Equipment	
e.	Overhead (15% of a, b, c) 10%	1,584.00
	Total	17,424.00

(See attached breakdown.)

7. Anticipated Duration of Work: Two years.

8. Facilities and Staff Available:

9. Additional Requirements:

10. Additional Information (Including relation of work to other projects and other sources of support):

Signature Roger K Lawson MD
Director of Project

Business Officer of the Institution H.L. Kaufmann, Administrator
Fresno County General Hospital

100101375

PROPOSED BUDGET PER ANNUM FOR TWO YEAR PROJECT

PERSONNEL		
Pulmonary fellowship (½ support of 4th year medical resident for work on project)		4,040.00
Technician full-time		6,000.00
Senior Clerk-Typist		4,800.00
SUPPLIES		1,000.00
	Subtotal	15,840.00
	+ 10% overhead	1,584.00
		$17,424.00

ADDENDUM

The criteria for diagnosis of chronic obstructive pulmonary disease, (C.O.P.D.) in the index cases and relatives will be a) a history of exertional dyspnea for at least one year, b) physical findings of obstructive airway disease such as expiratory wheezing on forced expiration, and c) pulmonary function abnormalities typical of obstruction -- in particular a F.E. V.1% below 70%, a midexpiratory flow rate (MMF) below 40% of the predicted value, a ratio of total lung capacity in liters to midexpiratory flow rate in liters/sec. of greater than 2 and a ratio of residual volume to total lung capacity of greater than 40%. Attempts will then be made to subclassify these cases into one of the following two categories:

a. Probable obstructive pulmonary emphysema (C.O.P.E.)

b. Probable chronic obstructive bronchitis (C.O.B.) without or with prominent bronchospasm ("asthmatic bronchitis")

Criteria for separation into these subgroups will be as follows:

A. Obstructive pulmonary emphysema -- all the criteria listed above for C.O.P.D. plus:

1. History: Relatively progressive or stable exertional dyspnea for at least one year.

2. Physical findings: Decreased breath sounds at both lung bases posteriorly, little expiratory wheezing.

3. X-ray: Attenuated vascular markings and/or prominent bullae on either conventional PA roentgenogram or tomograms.

4. Pulmonary function studies:

a. Evidence of expiratory collapse of bronchioles i.e. a ratio of midinspiratory flow rate to midexpiratory flow rate of > 2.5.

b. Reduction in single breath carbon monoxide diffusion capacity < 60% of predicted normal.

B. Obstructive bronchitis -- all the criteria listed above for C.O.P.D. plus:

1. History: Prominent productive or nonproductive cough. Intermittent nature of exertional dyspnea.

2. Physical findings: Normal intensity of breath sounds at bases posteriorly. Prominent expiratory wheezing.

3. X-ray: Normal vascularity and absence or dearth of bullae.

4. Pulmonary function:

a. Ratio of midinspiratory flow rate to midexpiratory flow rate of < 2.5.

b. Relatively normal single breath carbon monoxide diffusion capacity -- > 60% of predicted normal.

c. Significant response to bronchodilator drug.

Patients will be scored according to the chart on the next page, and classified according to the highest score. In case the scores are within two points difference, the case will be classified as indeterminate.

Attempts will be made to secure autopsies on any index case or relatives who expire during this study. Lungs will be fixed in the inflated state with liquid 10% formalin at 25-30 cm. of pressure. Gross and microscopic sections will be taken from these specimens and examined with dissecting and standard microscopes respectively.

Factors Favoring	(Chronic COPE Obstructive Pulmonary Emphysema)	Score	(Chronic COB Obstructive Bronchitis)	Score
History				
Dyspnea	Stable or Progressive	2	Intermittent	2
Cough	Mild	1	Prominent	1
Px				
Breath sounds	Diminished at bases	1	Normal	1
Wheezing	Absent	1	Prominent	1
X-ray				
Vascularity	Attenuated	1	Normal	1
Bullae	Prominent	1	Minimal	1
Function studies				
Midinspir. F.R. / Midexp. F.R.	> 2.5	2	< 2.5	2
$D_{LCO_{SB}}$	< 60% of normal	1	> 60% of normal	1
Response to Isuprel	Poor	1	Good	1

STANDARD HISTORY QUESTIONNAIRE

1. Name
2. Age
3. Sex
4. Relative of:
5. Relationship
6. Occupations
7. Childhood asthma
8. Pneumonia
9. Alcohol consumption
10. Smoking history
    a. Age started
    b. Types of smoking
    c. Average number of packs/day
    d. Still smoking
    e. Age stopped
11. Chronic cough
12. Sputum production
13. Hemoptysis
14. Chest pain
15. Dyspnea or Exertion
    a. Duration
    b. Stable
    c. Progressive
    d. Intermittent
    e. Amount of activity required to produce dyspnea
16. Wheeze
17. Family history (See additional form)

8. Facilities and staff available

The complete facilities of the pulmonary function laboratory at Fresno General Hospital will be used for this project. This laboratory is equipped with the following items:

2 13.5 L Collins spirometers with high speed kymographs

2 Collins Residual Volume Carts with helium analyzers - one with balloon in a box system for single breath CO diffusion capacity test

1 Beckman GC 2A gas chromatograph for N_2, O_2, CO_2, and CO analyses

1 Radiometer system for pCO_2, pO_2, and pH determination of arterial blood

1 Beckman Spinco system for pCO_2, pO_2, and pH determination of arterial blood

1 Scholander apparatus

1 Sanborn 2 channel recorder, pressure transducer and Collins spirometer potentiometer for measurement of pulmonary compliance.

In addition, other hospital facilities such as clinic, x-ray, and pathology will be utilized.

Name #	Age if Living	Age at Death	Emphysema	Asthma	Chronic Bronchitis	Lung Cancer	Chronic Cough	Chronic Dyspnea	Wheezing
Mother									
Father									
Brothers									
Sisters									
Sons									
Daughters									